ORIGINAL ARTICLE

Experience with belatacept rescue therapy in kidney transplant recipients

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SUMMARY

In kidney transplant recipients with chronic graft dysfunction, long-term immunosuppression with calcineurin inhibitors (CNIs) or mTOR inhibitors (mTORi) can be challenging due to adverse effects, such as nephrotoxicity and proteinuria. Seventy-nine kidney transplant recipients treated with CNI-based or mTORi-based maintenance immunosuppression who had CNI-induced nephrotoxicity or severe adverse events were switched to belatacept. Mean time from transplantation to belatacept conversion was 69.0 months. Mean estimated glomerular filtration rate (eGFR) ± standard deviation at baseline was 26.1 ± 15.0 ml/min/1.73 m^2, increasing to 34.0 ± 15.2 ml/min/1.73 m^2 at 12 months postconversion ($P < 0.0005$). Renal function improvements were also seen in patients with low eGFR (<25 ml/min/1.73 m^2) or high proteinuria (>500 mg/l) at conversion. The Kaplan–Meier estimates for patient and graft survival at 12 months were 95.0% and 85.6%, respectively. The discontinuation rate due to adverse events was 7.9%. One case of post-transplant lymphoproliferative disorder occurred at 17 months postconversion. For comparison, a historical control group of 41 patients converted to mTORi-based immunosuppression because of biopsy-confirmed CNI-induced toxicity was examined; eGFR increased from 27.6 ± 7.2 ml/min/1.73 m^2 at baseline to 31.1 ± 11.9 ml/min/1.73 m^2 at 12 months ($P = 0.018$). Belatacept-based immunosuppression may be an alternative regimen for kidney transplant recipients with CNI- or mTORi-induced toxicity.

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belatacept, calcineurin inhibitor, conversion, kidney transplantation, mTOR inhibitor

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Introduction

The calcineurin inhibitors (CNIs) cyclosporine and tacrolimus, as well as the mTOR inhibitors (mTORi) sirolimus and everolimus, are the standard of care for long-term immunosuppression in kidney transplant recipients (KTRs). However, CNIs can be nephrotoxic, which may accelerate kidney function decline and contribute to allograft loss [1–4]. In particular, in ageing allografts showing biopsy-confirmed chronic changes (often in combination with humoral damage), long-term use of CNIs may accelerate kidney function decline [3,5]. Although mTORi are not directly nephrotoxic, their use has been associated with worsening proteinuria and unfavourable outcomes in some KTRs [6,7]. New immunosuppressive strategies are needed to preserve graft function in KTRs [8].

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Treatment conversion has been examined in the early (≤6 months) [9,10] and late (>6 months) post-transplant periods [6,11–13]. Most studies have compared CNI-based with mTORi-based immunosuppression, representing the two main groups of immunosuppressive agents in use at the time of study initiation. In the late-stage setting, patients with poor renal function have been shown to experience limited benefit from mTORi conversion due to an increased incidence of adverse events (AEs) [11–13]. In the CONVERT study, which randomized CNI-treated KTRs to either continue CNI-based therapy or switch to sirolimus, enrolment of patients with glomerular filtration rate (GFR) 20–40 ml/min was halted for safety reasons [11]. Similarly, in *post hoc* analyses of ASCERTAIN, the difference in renal function between baseline and month 24 was significantly greater in patients who switched from CNI-based to mTORi-based therapy versus those who continued CNI-based treatment, but only in the subgroup of patients with a baseline creatinine clearance >50 ml/min [12]. Currently, no conversion scheme has been shown to benefit patients with ageing allografts who have been exposed to long-term immunosuppression and who exhibit declining graft function and/or proteinuria.

Belatacept, an intravenously administered selective T-cell co-stimulation blocker, is indicated for use as part of a CNI-free regimen [14]. Data from two randomized phase III studies of *de novo* KTRs (BENEFIT and BENEFIT-EXT) showed significantly greater GFR versus cyclosporine-based immunosuppression, although rates and grades of acute rejection (AR) were higher for belatacept in the first year post-transplant [15–22].

Belatacept conversion was examined in 173 CNI-treated patients with stable graft function (35–75 ml/min/1.73 m^2) randomized to continue CNI-based therapy or switch to belatacept-based immunosuppression at ≥6 to ≤36 months post-transplant. At month 12, patients who switched to belatacept had statistically significant improvements in kidney function; the safety profile of both regimens was similar [23]. While the safety and efficacy of switching to belatacept has been formally evaluated in patients with stable graft function, belatacept conversion in patients with graft dysfunction is limited to case series with <10 KTRs [24–27]. However, the available data support use of belatacept as rescue therapy.

This study summarizes safety and efficacy outcomes in 79 KTRs with chronic transplant nephropathy or CNI-induced nephrotoxicity and declining graft function switched from a CNI or mTORi to belatacept. This is the largest study of late-stage conversion to belatacept conducted to date.

Patients and methods

Study design and patients

This retrospective study analysed adult kidney transplant patients treated at two German transplant centres. The medical records of all patients treated with CNI-based or mTORi-based maintenance immunosuppression who switched to belatacept were reviewed. All patients who received ≥1 dose of belatacept were included. Transplant biopsies were obtained within 6 months prior to conversion and scored in a semi-quantitative manner per published criteria [28]. Chronicity scores, ranging from 0 to 12, derived from the sum of four basic 'chronic' Banff qualifiers (chronic glomerular damage, interstitial fibrosis, tubular atrophy and vascular intimal thickening) [29]. All patients were Epstein/Barr virus-positive, and women of child-bearing potential were required to use contraception.

Treatment

Belatacept 5 mg/kg was administered intravenously on days 1, 15, 29, 43 and 57 and then every 28 days thereafter as published for late-stage conversion [23]. For patients converting from CNI-based immunosuppression, cyclosporine or tacrolimus dose was tapered as follows: 100% on day 1, 40–60% on day 2, 20–30% on day 15 and 0% on day 29 and beyond. For patients converting from mTORi-based immunosuppression, sirolimus or everolimus dose was tapered as follows: 100% on day 1, 50–75% on day 2, 25–50% on day 15 and 0% on day 29 and beyond. Any adjunctive immunosuppressive or corticosteroids treatments were maintained at existing doses unless modification was medically necessary (i.e. steroid dose was not tapered). In patients with CNI-induced thrombotic microangiopathy (TMA), CNI was stopped immediately, with belatacept 10 mg/kg administered on days 1, 5, 14 and 28 followed by belatacept 5 mg/kg every 28 days thereafter.

Outcomes

The co-primary end points were the changes in estimated GFR (eGFR; Modification of Diet in Renal Disease formula [30]) from baseline to month 6 and baseline to month 12. Secondary end points included the incidence of biopsy-confirmed AR, patient and graft survival, proteinuria, serum lipid levels, glycated haemoglobin levels and safety. Patients with clinically suspected AR underwent renal biopsy. Depending on the time of diagnosis, biopsies were classified according to

Banff '07, Banff '09 or Banff '13 criteria [28,31,32] and treated per local practice. AEs were mapped to MedDRA version 12.1 and recorded throughout belatacept treatment. Because of this study's retrospective design, only grade ≥2 AEs were recorded. The presence of anti-donor human leucocyte antibodies at baseline was assessed by local laboratory using Luminex® [33].

Controls

Because of the heterogeneity of indications for conversion to belatacept, the subgroup of patients converted to belatacept because of CNI toxicity was compared to a historical control cohort of patients from Charite Campus Mitte who were converted to mTORi-based immunosuppression between 2005 and 2011 (before approval of belatacept) because of histologically confirmed CNI-induced toxicity. Control patients had an eGFR <40 ml/min at conversion.

Statistical analysis

Efficacy and safety were analysed in patients who received ≥1 dose of belatacept until 30 November 2014. Mixed linear models with a first-order autoregressive covariance structure were calculated for eGFR. Explanatory variables were eGFR0 (before conversion) and categorical time (3, 6 and 12 months); the dependent variable was eGFR (values at 3, 6 and 12 months). The initial model only included data from belatacept-treated patients. Data from the historical control cohort were added to a second model so that differences in eGFR could be compared following belatacept-based or mTORi-based conversion therapy. Secondary end points were summarized descriptively. Survival, exposure to belatacept and time on treatment were analysed according to Kaplan–Meier with a log-rank test, if applicable. Missing values at 6 and 12 months postconversion were imputed using last observation carried forward (LOCF) analysis and results are shown in all figures, but were not included in the statistical analysis. Statistical analyses were performed using SPSS for Windows release 22.0.0 (SPSS Inc., Chicago, IL, USA). The end of observation was 31 May 2015.

Results

Belatacept conversion cohort

Patient disposition

Seventy-nine patients were converted to belatacept. Patients had been transplanted on average 69.0 months prior to conversion (Table 1). The most common reason for conversion was biopsy-confirmed CNI-induced nephrotoxicity (51.9%). The majority converted to belatacept from tacrolimus (50.6%) followed by cyclosporine (21.5%), everolimus (20.2%) and sirolimus (7.6%; Table 1). Of the 22 patients who received mTORi-based immunosuppression prior to belatacept conversion, 17 had been previously switched from CNI-based to mTORi-based therapy because of histologically confirmed CNI-induced nephrotoxicity.

Sixty-five (82.3%) patients were biopsied within 6 months prior to conversion; the distribution of chronicity scores (as markers for chronic transplant damage) is shown in Table S1. Twenty-four (30.4%) patients experienced AR prior to conversion (grade IA, $n = 10$; grade IB, $n = 2$; grade IIA, $n = 6$; grade IIB, $n = 3$; acute humoral, $n = 3$); of these, 10 (12.7%) had biopsy-confirmed rejection within 6 months of conversion.

Median exposure time to belatacept was 13 months with a 25th and 75th percentile range of 7–19 months (Fig. S1).

Glomerular filtration rate

Over 12 months of follow-up, the mixed linear model showed significant effects for the changes in eGFR relative to baseline. Mean eGFR (±SD) at conversion (baseline) was 26.1 ± 15.0 ml/min/1.73 m^2. Mean eGFR increased significantly to 29.7 ± 15.0 at 3 months ($P = 0.002$), 31.6 ± 14.5 at 6 months ($P < 0.0005$) and 34.0 ± 15.2 ml/min/1.73 m^2 at 12 months postconversion ($P < 0.0005$; Fig. 1). eGFR estimates deriving from the mixed linear model are presented in Table S2.

In patients with GFR <25 ml/min/1.73 m^2 at conversion ($n = 44$), mean eGFR at baseline was 17.2 ± 5.1 ml/min/1.73 m^2. Mean eGFR at 3, 6 and 12 months postconversion was 22.2 ± 10.3, 25.6 ± 10.9 and 27.3 ± 13.1 ml/min/1.73 m^2, respectively. Each of these means differed significantly from the mean eGFR at baseline ($P = 0.004$, $P < 0.0001$ and $P < 0.0001$, respectively; Fig. 1). In patients with GFR >25 ml/min/1.73 m^2 at conversion ($n = 35$), mean eGFR prior to conversion was 37.4 ± 15.8 ml/min/1.73 m^2. Mean eGFR at 3, 6 and 12 months postconversion was 39.0 ± 14.8, 38.8 ± 15.3 and 41.8 ± 13.5 ml/min/1.73 m^2, respectively; the increase in mean eGFR between baseline and month 12 was significant ($P = 0.001$; Fig. 1).

Among those patients who were DSA-positive at the time of conversion ($n = 27$), mean eGFR at baseline was 24.0 ± 2.0 ml/min/1.73 m^2. Mean eGFR at 3, 6 and 12 months postconversion was 26.8 ± 2.0,

Table 1. Patient characteristics at the time of conversion.

Patient characteristics	Conversion to belatacept (n = 79)	Conversion to mTORi* (n = 41)	P value
Mean age ± SD, years	53.9 ± 14.7	52.9 ± 11.9	0.70
Mean time after transplantation ± SD, months	69.0 ± 62.6	51.5 ± 55.3	0.11
Male, n (%)	48 (60.8)	30 (73.2)	
Mean eGFR ± SD, ml/min/1.73 m^2	26.1 ± 15.0	27.6 ± 7.2	0.47
Treatment prior to conversion, n (%)			
Tacrolimus	40 (50.6)	7 (17.1)	0.42
Mean trough level ± SD	4.8 ± 1.8	5.8 ± 0.21	
Cyclosporine	17 (21.5)	34 (82.9)	0.025
Mean trough level ± SD	72.2 ± 13.8	93.8 ± 31.8	
Everolimus	16 (20.3)	N/A	
Mean trough level ± SD	4.7 ± 1.3		
Sirolimus	6 (7.6)	N/A	
Mean trough level ± SD	5.1 ± 1.4		
Reason for conversion, n (%)			
From a CNI	57 (72.2)	41 (100)	N/A
CNI-induced toxicity	41 (51.9)	41 (100)	
Only CNI-induced toxicity	9 (11.4)	36 (87.8)	
CNI-induced toxicity plus DSA positivity	15 (19)	3 (7.3)	
CNI-induced toxicity plus DSA positivity plus history of humoral rejection	3 (3.8)	0 (0)	
CNI-induced toxicity plus history of cellular rejection	9 (11.4)	2 (4.9)	
CNI-induced toxicity plus history of cellular rejection plus DSA positivity	5 (6.3)	0 (0)	
Severe CNI-induced adverse event	12 (15.2)	0 (0)	
Thrombotic microangiopathy	4 (5.1)	0 (0)	
Neurotoxicity	4 (5.1)	0 (0)	
Delayed graft function	3 (3.8)	0 (0)	
Post-transplant distal limb syndrome	1 (1.3)	0 (0)	
Compliance†	4 (5.1)	0 (0)	
From an mTORi	22 (27.8)	N/A	N/A
Severe mTORi-induced adverse event	22 (27.8)		
History of CNI-induced toxicity‡ and cellular rejection	7 (8.9)		
History of CNI-induced toxicity‡ and DSA positivity	6 (7.6)		
Proteinuria‡	6 (7.6)		
Dyslipoproteinemia/NODAT	3 (3.8)		
Tremor	1 (1.3)		

CNI, calcineurin inhibitor; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor; N/A, not applicable; NODAT, new onset diabetes after transplantation; SD, standard deviation.

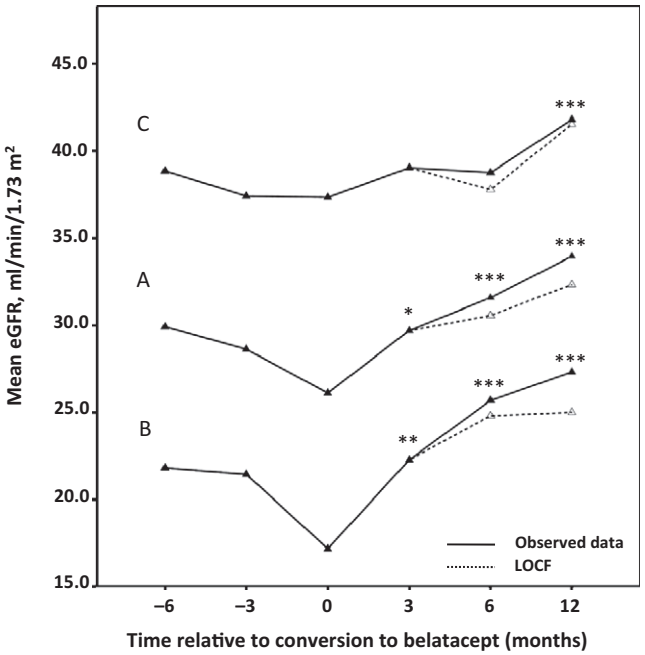
*Historical control cohort.

†One patient suffered from severe depression (including suicidal attempts), one had been transplanted as a child and had a history of noncompliance, one had recurrent, documented CNI trough levels below the detection limit, and one subjectively experienced drug intolerance with almost all immunosuppressive regimens (resulting in frequent unauthorized changes in medication).

‡A total of 17 patients who converted from an mTORi to belatacept, including four of the patients presenting with proteinuria, had been previously converted from a CNI to an mTOR because of histologically confirmed CNI-induced toxicity.

29.2 ± 2.2 and 34.5 ± 2.6 ml/min/1.73 m^2, respectively. The increase in mean eGFR relative to baseline reached statistical significance at 12 months postconversion ($P < 0.05$).

Among patients using an mTORi prior to conversion (n = 22), mean eGFR at baseline was 32.3 ± 20.5 ml/min/1.73 m^2. Mean eGFR increased to 34.0 ± 17.1, 35.4 ± 18.0 and 38.4 ± 11.1 ml/min/1.73 m^2 at 3, 6 and



A) Belatacept all patients	*N* =	61	69	79	79	71	48
B) Belatacept GFR<25 ml/min	*N* =	32	37	44	44	40	27
C) Belatacept GFR>25 ml/min	*N* =	29	32	35	35	31	21

Figure 1 Mean eGFR before and after conversion to belatacept (A) in all study participants ($n = 79$); (B) in the subgroup of patients with GFR values <25 ml/min/1.73 m^2 at the time of conversion ($n = 44$); (C) in the subgroup of patients with GFR values >25 ml/min/1.73 m^2 at the time of conversion ($n = 35$). *P*-values for changes from baseline derived from a mixed linear model. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. eGFR, estimated glomerular filtration rate.

12 months postconversion, respectively. The increases in mean eGFR between baseline and months 6 and 12 postconversion were significant ($P = 0.025$ and $P < 0.0001$, respectively; Fig. 2). In patients using a CNI prior to conversion ($n = 57$), mean eGFR at baseline was 23.6 ± 11.7 ml/min/1.73 m^2, increasing significantly to 27.9 ± 13.9 ($P = 0.005$), 29.5 ± 12.5 ($P = 0.002$) and 32.3 ± 16.6 ml/min/1.73 m^2 ($P < 0.0001$) at 3, 6 and 12 months postconversion, respectively (Fig. 2).

In patients with proteinuria <500 mg/l at conversion ($n = 57$), mean eGFR at baseline was 28.4 ± 16.3 ml/min/1.73 m^2. Mean eGFR increased significantly to 31.1 ± 15.8 ml/min/1.73 m^2 at 3 months postconversion ($P = 0.031$), 33.0 ± 15.4 ml/min/1.73 m^2 at 6 months postconversion ($P = 0.017$) and 35.7 ± 14.6 ml/min/1.73 m^2 at 12 months postconversion ($P < 0.001$; Fig. 3). In patients with proteinuria >500 mg/l at conversion ($n = 22$), mean eGFR at baseline was 20.4 ± 8.2 ml/min/1.73 m^2, while mean eGFR at 3, 6 and 12 months postconversion was 26.0 ± 12.2, 27.5 ± 11.0 and 29.2 ± 16.1 ml/min/1.73 m^2, respectively. Compared with baseline, the increases in mean eGFR were significant at 3, 6 and 12 months postconversion ($P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively; Fig. 3).

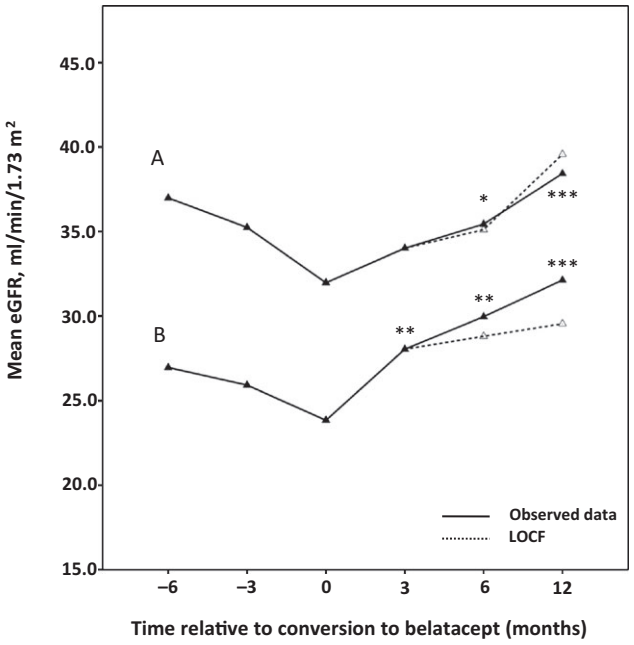
Missing values

At 12 months after conversion, 31 of 79 (39.2%) values were missing; 11 patients experienced graft loss or died, and 20 patients had not yet completed follow-up. To estimate the effect of missing values, LOCF analyses were performed and results were depicted in all figures without statistical analysis. All results of LOCF analysis are given in Table S3.

Proteinuria

Across all study participants, mean proteinuria (±SD) at baseline was 413 ± 546 mg/l. Proteinuria levels decreased to 361 ± 448 mg/l at 3 months, 328 ± 433 mg/l at 6 months and 255 ± 214 mg/l at 12 months postconversion. These changes did not differ significantly versus baseline.

In patients using an mTORi prior to conversion ($n = 22$), mean proteinuria decreased from



A) Conversion from mTORi	*N* =	18	20	22	22	21	14
B) Conversion from CNI	*N* =	43	49	57	57	50	34

Figure 2 Mean eGFR before and after conversion (A) in the subgroup of patients switching from an mTORi to belatacept ($n = 22$); (B) in the subgroup of patients switching from a CNI to belatacept ($n = 57$). $^{**}P < 0.01$, $^{***}P < 0.001$. CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor.

331 ± 559 mg/l at baseline to 244 ± 345, 183 ± 224 and 98 ± 130 mg/l at 3, 6 and 12 months postconversion, respectively. The decrease in mean proteinuria at months 3, 6 and 12 postconversion differed significantly from the mean at baseline ($P = 0.044$, $P = 0.001$, and $P = 0.001$, respectively; Fig. S2). In patients with proteinuria levels >500 mg/l at conversion ($n = 22$), mean proteinuria decreased from 1046 ± 686 mg/l at baseline to 747 ± 563, 719 ± 655 and 305 ± 218 mg/l at 3, 6 and 12 months postconversion. The decreases in proteinuria were significant versus baseline at all time points (Fig. S2).

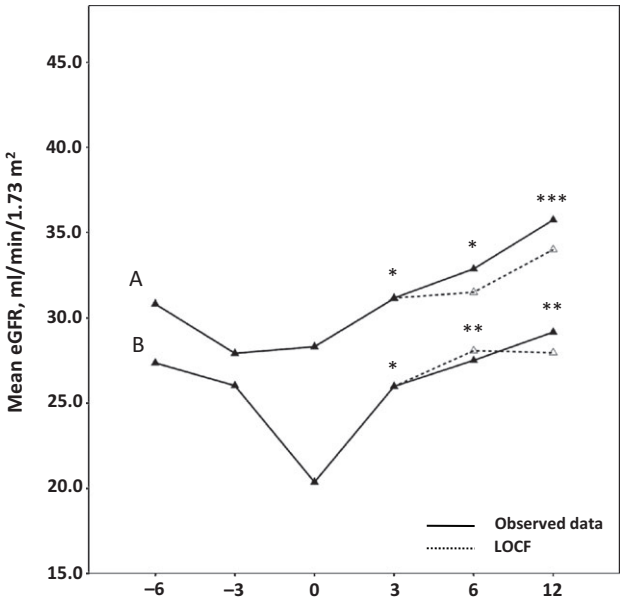
Cholesterol and HbA1c

In total, 73 patients had cholesterol measurements available at both baseline and month 6 postconversion. Compared with baseline, cholesterol levels were significantly lower at 6 months postconversion (214.7 ± 73 vs. 197.3 ± 47 mg/dl, $P < 0.01$). A total of 53 patients had HbA1c values available at both baseline and month 6 postconversion. No significant changes in HbA1c levels were observed (baseline, 5.66 ± 0.8%; month 6 postconversion, 5.42 ± 0.8%; $P = 0.054$).

Graft and patient survival

The Kaplan–Meier estimates for graft survival at 6 and 12 months postconversion were 93.6% and 85.6%, respectively, and include three patients who died with a functioning graft (Fig. 4). Two patients died as a consequence of myocardial infarction and one died owing to non-small-cell lung carcinoma (NSCLC). Of the eight patients who lost their graft in the first year postconversion, five (62.5%) were DSA-positive at baseline and had a baseline eGFR of 21.9 ± 8.9 ml/min/1.73 m^2 and baseline proteinuria of 697 ± 722 mg/l. Graft loss in the first year was attributable to fulminant rejection ($n = 2$) and chronic graft failure ($n = 6$).

Four patients were switched to belatacept due to CNI-induced TMA, diagnosed at 1, 6, 18 and 47 months post-transplant. The patient switched to belatacept at 47 months post-transplantation showed impaired graft function at conversion and experienced graft failure at 9 months postconversion without clinical signs of active haemolytic uremic syndrome. Renal function in the other three patients recovered fully following belatacept conversion.



A) PU before conversion <500 mg/l	*N* =	45	54	57	57	50	35
B) PU before conversion >500 mg/l	*N* =	16	15	22	22	21	13

Figure 3 Mean eGFR before and after conversion to belatacept (A) in the subgroup of patients with proteinuria levels <500 mg/l at the time of conversion (n = 57); (B) in the subgroup of patients with proteinuria levels >500 mg/l at the time of conversion (n = 22). *P < 0.05, **P < 0.01, ***P < 0.001. eGFR, estimated glomerular filtration rate.

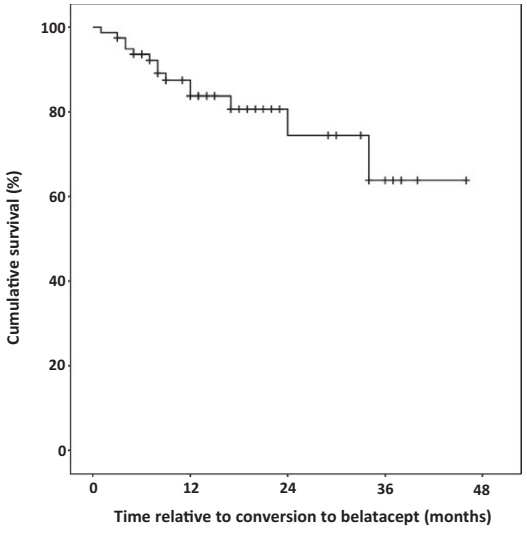
Acute rejection

Nine (11.4%) patients experienced biopsy-confirmed AR (grade IB, n = 4; grade IIA, n = 1; grade IIB, n = 3; grade III, n = 1), with two graft losses due to fulminant rejection. Of the nine patients presenting with AR, three switched to belatacept because of compliance issues.

Safety

Most grade ≥2 AEs occurred in system organ class 'infections and infestations' (Table 2). The majority of reported viral (14/18, 77.8%) and bacterial infections (31/49, 63.3%) were grade 2. Anaemia was the most common haematological disorder; all but two events were grade 2. Seven (7.9%) patients discontinued belatacept due to an AE [fulminant rejection postconversion, n = 2; Kaposi's sarcoma, n = 1; miliary tuberculosis, n = 1, cytomegalovirus-related disease, n = 1; central nervous system post-transplant lymphoproliferative disorder (CNS PTLD), n = 1; hyponatremia, n = 1].

Thirty-three (41.8%) patients were hospitalized for a total of 57 serious AEs, most commonly infection (see Table 2). Twelve of the 19 reported infections were severe



Patients	*N* =	79	48	12	5	1
Death	*N* =		3	3	3	3
Graft loss	*N* =		8	10	11	11

Figure 4 Kaplan–Meier curve for the time to death or graft loss.

(urosepsis, n = 6; cytomegalovirus, n = 2; *Pneumocystis jirovecii* pneumonia, n = 1; miliary tuberculosis, n = 1; phlegmon, n = 1; *Candida* septicaemia, n = 1). Four

Table 2. Summary of safety events occurring following conversion to belatacept (cumulative exposure of 1214 months).

Grade ≥2 AEs	Events, *n*	Number of events per month of exposure
Infections and infestations		
Viral	18 events in 18 patients	0.015
Grade 2 (oral intervention)	14	
Grade 3 (intravenous intervention)	2	
Grade 4 (life-threatening)	2	
Bacterial	49 events in 40 patients	0.04
Grade 2 (oral intervention)	31	
Grade 3 (intravenous intervention)	15	
Grade 4 (life-threatening)	3	
Fungal and other*	7 events in 7 patients	0.006
Grade 2 (oral intervention)	4	
Grade 3 (intravenous intervention)	0	
Grade 4 (life-threatening)	3	
Blood and lymphatic system disorders		
Anaemia	36 events in 28 patients	0.03
Grade 2 (haemoglobin <10 g/dl or increase/ start erythropoiesis-stimulating agents)	34	
Grade 3 (haemoglobin <8 g/dl or transfusion)	1	
Grade 4 (life-threatening)	1	
Leukopenia	18 events in 17 patients	0.015
Grade 2 (<3000 to 2000 cells/mm^3)	11	
Grade 3 (<2000 to 1000 cells/mm^3)	4	
Grade 4 (<1000 cells/mm^3 or <500 neutrophils/mm^3)	3	
Thrombocytopenia	2 events in 2 patients	0.002
Grade 2 (<75,000 to 50,000 platelets/mm^3)	1	
Grade 3 (<50,000 to 25,000 platelets/mm^3)	1	
Grade 4 (<25,000 platelets/mm^3, bleeding)	0	
Gastrointestinal disorders	11 events in 11 patients	0.009
Grade 2 (outpatient treatment)	6	
Grade 3 (hospitalization)	3	
Grade 4 (life-threatening)	2	
Cardiac disorders	5 events in 5 patients	0.004
Grade 2 (symptomatic, progressive angina, hemodynamically stable)	2	
Grade 3 (symptomatic, unstable angina or acute myocardial infarction, hemodynamically stable)	1	
Grade 4 (symptomatic unstable angina and/or acute myocardial infarction, hemodynamically unstable)	0	
Grade 5 (death)	2†	
Serious AEs requiring hospitalization	57 events in 33 patients	0.047
Infection	19	
Acute rejection	9	
Prerenal acute renal failure	6	
Cardiovascular	4	
Malignancy	4	
Other‡	15	
Death	3§	

AE, adverse event.

*Other includes tuberculosis and *Pneumocystis jirovecii*.

†Death due to myocardial infarction. One patient died 2 months postconversion, and the other died 8 months postconversion.

‡Other includes haematological disorders, gastrointestinal disorders and trauma.

§Total includes the two patients who died from myocardial infarction plus one additional patient who died from non-small-cell lung carcinoma.

patients developed a malignancy [NSCLC (9 months postconversion), Kaposi's sarcoma (8 months postconversion), basal cell carcinoma (4 months postconversion) and CNS PTLD (17 months postconversion)]. Forty-six patients were not hospitalized during belatacept-based treatment.

Historical control cohort

Patient disposition

The historical control cohort was composed of 41 patients converted to mTORi-based immunosuppression because of histologically confirmed CNI-induced toxicity. Patients had been transplanted on average 51.5 months prior to conversion. The majority converted from cyclosporine (82.9%; Table 1) with 37 (90.2%) patients converting to everolimus and four (9.8%) converting to sirolimus. All patients were biopsied before conversion; of these, 31 (75.6%) had been biopsied in the 6 months prior to conversion. The distribution of chronicity scores is shown in Table S1. Two (4.9%) patients experienced Banff grade IIA AR 6 months prior to conversion, and one (2.4%) had biopsy-confirmed Banff grade IA AR within 6 months postconversion.

Efficacy

Mean eGFR (±SD) at conversion was 27.6 ± 7.2 ml/min/1.73 m^2. Relative to baseline, mean eGFR increased to 31.1 ± 10.2 ml/min/1.73 m^2 at 3 months, 32.2 ± 13.2 ml/min/1.73 m^2 at 6 months and 31.1 ± 11.9 ml/min/1.73 m^2 at 12 months postconversion ($P = 0.006$, $P = 0.001$ and $P = 0.018$, respectively). At 12 months postconversion, changes in eGFR from baseline were not significantly different in patients who converted to belatacept-based versus mTORi-based immunosuppression because of CNI-induced toxicity ($P = 0.12$; Fig. 5).

Mean proteinuria (±SD) at baseline was 118 ± 116 mg/l. Proteinuria increased to 143 ± 179 mg/l at 3 months, 171 ± 199 mg/l at 6 months and 306 ± 403 mg/l at 12 months postconversion. The increase in mean proteinuria relative to baseline reached significance at 12 months postconversion ($P < 0.0001$). One patient died of myocardial infarction within 1 year of conversion, and no graft loss was reported. Thus, the patient and graft survival rate at 12 months postconversion was 97.2%. Seven patients (17.1%) discontinued mTORi-based therapy due to AEs within 1 year of conversion (pneumonitis $n = 3$, disturbed wound healing $n = 1$, sepsis $n = 1$, proteinuria $n = 1$, rejection Banff IA $n = 1$). AEs documented in the first 12 months after conversion are shown in the Table S4. Time on mTORi-based immunosuppression compared to belatacept-based immunosuppression was similar in both groups (log-rank: $P = 0.55$) and is shown in the Fig. S3.

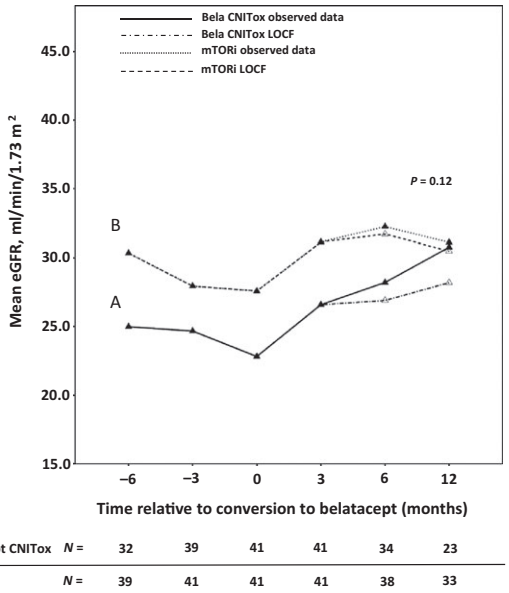


Figure 5 Comparison of eGFR in patients with CNI-induced toxicity converted to belatacept-based ($n = 41$) or mTORi-based immunosuppression ($n = 41$). CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; mTORi, mammalian target of rapamycin inhibitor.

Discussion

This retrospective analysis examined late-term conversion from a CNI or mTORi to belatacept in 79 difficult-to-treat patients with histologically confirmed CNI-induced nephrotoxicity, severe chronic vascular damage, severe CNI- or mTORi-related AEs or compliance issues. Belatacept conversion was associated with both statistically and clinically significant improvements in eGFR (mean increase of 7.9 ml/min/1.73 m^2 at 12 months postconversion versus baseline). Renal function also improved in the subgroups of patients with either low eGFR (<25 ml/min/1.73 m^2) or high proteinuria (>500 mg/l) at conversion. At 12 months postconversion, the Kaplan–Meier estimates for patient and graft survival were 95.0% and 85.6%, respectively. These results become more striking when one considers the timing of conversion (mean, 69.0 months post-transplant) and that patients were approaching the need to return to dialysis (mean eGFR at conversion, 26.1 ml/min/

1.73 m^2). However, two patients lost their graft shortly after belatacept conversion due to fulminant rejection, which is consistent with the increased rates of AR observed in *de novo* belatacept-treated patients [15,19]. Of the nine episodes of AR observed in the present analysis, three occurred in patients converted to belatacept due to compliance issues. Because it is administered intravenously, belatacept may appear to be an attractive therapeutic option for KTRs with compliance issues, but our results – although deriving from only a few patients – raise concerns about converting poorly adherent patients to belatacept.

Our findings complement those from a phase II study of renal transplant recipients with stable graft function (mean eGFR at baseline, 53.5 ml/min/1.73 m^2) who were randomized to continue CNI-based immunosuppression or switch to belatacept-based immunosuppression [23]. At 12 months postconversion, the switch to belatacept was associated with a mean increase in eGFR of 7.0 ml/min/1.73 m^2. None of the 83 belatacept-treated patients in the phase II study died or lost their graft, but six (7.1%) experienced AR; all cases resolved [23]. As in previous studies [15,19], these AR episodes occurred soon after initiating belatacept. The rate of acute viral infections in the present study was higher than in the phase II study (22.8% vs. 13.3%) [23]. Three patients in our study developed life-threatening malignancies (CNS PTLD, NSCLC and Kaposi's sarcoma) compared with one case of Kaposi's sarcoma in the phase II study [23]. The AE profile in the present study may be a consequence of the older age of our cohort (53.8 vs. 45.3 years) and the longer time spent on immunosuppression (69.0 vs. 19.4 months). More data are needed to better define the risk of infections and malignancies after belatacept conversion.

The majority of patients (94.9%) in our study were switched to belatacept due to treatment-related toxicities or AEs associated with CNI-based or mTORi-based immunosuppression, and more than half (55.7%) had eGFR <25 ml/min/1.73 m^2. Despite the characteristics of this population, the switch to belatacept was generally well-tolerated by most patients, with a low rate of treatment discontinuations due to AEs (7.9%). This is notable, as eGFR >40 ml/min and lower histological scores for chronic allograft nephropathy have been found to be predictive of successful conversion from CNI-based to sirolimus-based immunosuppression, conversion in patients with low eGFR has been associated with safety concerns [11,34], and additionally, conversion to mTORi-based immunosuppression has been found to benefit only those patients with proteinuria levels <800 mg/l at conversion [6]. Thus, the present study is the first to demonstrate improvements in renal function in patients with graft dysfunction or proteinuria.

Our data are biased by a high rate of missing values at 12 months postconversion. Although LOCF analyses still show a trend to eGFR improvement, long-term analyses of outcomes are needed to better evaluate the effect of rescue conversion to belatacept.

Chronic humoral rejection – clinical and subclinical – has an adverse impact of graft survival, with DSA-positive KTRs at high-risk of graft loss [35–38]. At 7 years post-transplant, rates of *de novo* DSA development were significantly lower in belatacept-treated versus cyclosporine-treated patients [18,22]. In the subgroup of patients in our analysis who were DSA-positive at baseline (n = 27), belatacept appeared to stabilize transplant function in the year after conversion. Although absolute numbers of patients are too small to draw conclusions, belatacept may benefit DSA-positive KTRs.

In our study, 22 (27.8%) patients were converted from an mTORi to belatacept. In this subgroup, both eGFR and proteinuria improved significantly following conversion. The development of proteinuria following kidney transplantation is negatively predictive of post-transplant outcomes, including patient and graft survival [6,39,40]. An examination of a larger number of patients is needed to ascertain whether belatacept conversion benefits patients who develop proteinuria.

Cardiovascular risk factors influence patient and graft survival [41–43]. In this analysis, significant improvements in serum cholesterol were demonstrated 6 months after conversion to belatacept. Together with the significant changes in eGFR and proteinuria, belatacept conversion resulted in an improved cardiovascular risk profile, supporting previous findings [17,19–21,40].

Four patients were converted to belatacept because of CNI-induced TMA; three of these patients exhibited a complete recovery in renal function, suggesting that belatacept may serve as an alternative immunosuppression regimen for patients with this rare – but often difficult to manage – post-transplant complication.

Because of the heterogeneity of patients converted to belatacept in this analysis and the difficulty in identifying matching controls, we compared the subgroup of patients converted to belatacept because of CNI-induced toxicity to a historical control cohort consisting of patients converted to mTORi-based immunosuppression because of histologically confirmed CNI-induced toxicity. eGFR significantly improved after conversion in both cohorts. However, at 12 months postconversion,

no statistically significant differences in changes from baseline between both groups could be demonstrated. Notably, chronicity scores (and therefore chronic transplant damage) were less severe in the historical control cohort versus the cohort of patients who converted to belatacept. Additionally, proteinuria increased significantly following mTORi conversion but decreased following belatacept conversion, and discontinuation rates owing to AEs in the first year after conversion were higher in patients switched to mTORi-based (17.1%) versus belatacept-based immunosuppression (7.6%). These results suggest that conversion to belatacept may be similar to other treatment concepts and may serve as an alternative immunosuppressive regimen, particularly for patients with higher grades of chronic transplant damage, patients in whom mTORi-based treatment is contraindicated, and/or patients whose immunological risk profile does not favour mTORi conversion. However, there is a need to evaluate long-term outcome in larger cohorts with regard to risk of rejection and infection following belatacept conversion in a larger number of KTRs.

Authorship

All authors contributed substantially to the design, performance, analysis and reporting of these results.

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Conflicts of interest

SB has received honoraria and travel grants from Bristol–Myers Squibb, Novartis, Roche, Pfizer and Alexion Astellas; MD has received research funds from Bristol–Myers Squibb and travel grants from Novartis and Roche; MW has received honoraria and travel grants from Bristol–Myers Squibb, Alexion, Chiesi and Astellas; KB has received research funds and/or honoraria from Alexion, Astellas, Bristol–Myers Squibb, Chiesi, Fresenius, Genentech, Hexal, Novartis, Otsuka, Pfizer, Roche, Siemens and Veloxis Pharma; DK, TB, FB and DS have nothing to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Kaplan–Meier curve of exposure time to belatacept.

Figure S2. Mean proteinuria levels before and after conversion.

Figure S3. Kaplan–Meier curve of time on mTORi-based immunosuppression compared to belatacept-based immunosuppression.

Table S1. Semi-quantitative biopsy scoring.

Table S2. Effect comparison in mixed linear models for eGFR.

Table S3. Results of LOCF analysis of eGFR.

Table S4. Summary of safety events occurring in the first 12 months following conversion to mTOR (cumulative exposure of 455 months).

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